CLAIMS

1. A method of generating a pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds comprising the steps of

(i) generating a set of three-dimensional conformers for each of the compounds in a training set comprising five or more selective serotonin reuptake inhibitor compounds;

(ii) correlating each of the compounds of said training set with an observed value for CYP2D6 inhibitory potency;

(iii) generating from the conformers of step (i) a set of one or more pharmacophore test models, each said pharmacophore test model comprising three or more of the CYP2D6 enzyme active site features selected from the group consisting of the hydrogen bond donor feature, the hydrogen bond acceptor feature, the hydrophobic region feature, the ionizable region feature and the ring aromatic feature, arranged in three-dimensional space;

(iv) calculating the CYP2D6 inhibitory potency for each conformer generated in step (i) towards each of the pharmacophore test models generated in step (iii);

(v) calculating the total cost for each pharmacophore test model; and

(vi) choosing the lowest cost pharmacophore test model as the pharmacophore model.

2. The method of claim 1 wherein the steps are carried out using a molecular modeling software.

3. The method of claim 1 wherein the steps are carried out with the molecular modeling software CATALYST™, version 4.

4. The method of claim 1 wherein the training set of selective serotonin reuptake inhibitor compounds are chosen from selective serotonin reuptake inhibitor compounds with observed CYP2D6 $K_{i\,(apparent)}$ values spanning at least three orders of magnitude.

5. The method of claim 4 wherein the observed CYP2D6 $K_{I\ (apparent)}$ values vary from 0.1 μM to 100 μM.

6. The method of claim 1 wherein the number of conformers in step (i) is limited to 255 conformers.

7. The method of claim 1 wherein the energy range of the conformers in step (i) is 50 Kcal/mole.

8. The method of claim 1 wherein the energy range of the conformers in step (i) is 35 Kcal/mole

9. The method of claim 1 wherein the energy range of the conformers in step (i) is 10 Kcal/mole.

10. The method of claim 1 wherein the training set of step (i) contains at least 10 compounds.

11. The method of claim 1 wherein the training set of step (i) contains at least 14 compounds.

12. The method of claim 1 wherein the training set of step (i) contains one or more compounds selected from the group consisting of: (*d,l*)-2-methoxy-4,5-methylenedioxyamphetamine; (*d,l*)-3,4-methylenedioxymethamphetamine; (*d,l*)-3,4-methylenedioxyamphetamine; (*d,l*)-3-methoxy-4,5-methylenedioxyamphetamine; (*d,l*)-2-methoxyamphetamine; (*d,l*)-3-methoxyamphetamine; (*d,l*)-4-methoxy-amphetamine; (+)-methamphetamine; (+)-amphetamine; (*d,l*)-2,4,6-trimethoxy-amphetamine; (*d,l*)-4-hydroxymethamphetamine; (*d,l*)-3,4,5-trimethoxyamphetamine; (+)-4-hydroxyamphetamine; and (*d,l*)-cathinone.

13. The method of claim 1 wherein at least 10 pharmacophore test models are generated in step (ii).

14. A method for screening an selective serotonin reuptake inhibitor compound for CYP2D6 inhibitory potency comprising the steps of:

(i) finding the optimum fit of the selective serotonin reuptake inhibitor compound to the pharmacophore model of claim 1; and

(ii) calculating a CYP2D6 inhibitory potency value for the selective serotonin reuptake inhibitor compound.

15. The method of claim 14 wherein finding the optimum fit in step (i) is carried out via the use of a fast-fit algorithm, a principle component analysis, a partial least squares technique, a linear regression technique or a non-linear regression technique.

16. A method of generating a pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds comprising the steps of

(i) correlating the chemical features of the conformers of the compounds in a training set of selective serotonin reuptake inhibitor compounds with a set of two- and/or three-dimensional descriptors for the active site of the CYP2D6 enzyme; and

(ii) generating an equation relating the observed CYP2D6 inhibitory potency of said selective serotonin reuptake inhibitor compounds to a set of generated two- and/or three dimensional descriptors for the selective serotonin reuptake inhibitor compound.

17. The method of claim 16 wherein the steps are carried out using the set of two- and/or three-dimensional descriptors for selective serotonin reuptake inhibitor compounds chosen from the 3D-QSAR functionality and the genetic function approximation equation of the CERIUS$^{2\,TM}$ software program.

18. The method of claim 16 wherein the CYP2D6 inhibitory potency is a value determined by *in vitro* of the inhibition of the CYP2D6 enzyme reaction with bufuralol, said value selected from the group consisting of the IC_{50} value, the % inhibition value or the $K_{I\,(apparent)}$ value.

19. The method of claim 16 wherein the CYP2D6 is native or recombinant CYP2D6.

20. A method for determining the CYP2D6 inhibitory potency of an selective serotonin reuptake inhibitor compound comprising the steps of

(i) generating the two- and/or three-dimensional descriptors for said selective serotonin reuptake inhibitor compound;

(ii) inputting said three-dimensional descriptors into an equation relating the observed CYP2D6 inhibitory activity of a set of selective serotonin reuptake inhibitor compounds to a set of three-dimensional descriptors generated for those selective serotonin reuptake inhibitor compounds; and

(iii) solving said equation for the CYP2D6 inhibitory activity of the selective serotonin reuptake inhibitor compound corresponding to the generated three-dimensional descriptors of step (i).

21. The method of claim 20 wherein steps (i) through (iii) are carried out using a software program.

22. The method of claim 21 wherein the software program is the CERIUS$^{2\,TM}$ program

23. A pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds generated in accordance with the method of claim 1.

24. A pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds generated in accordance with the method of claim 16.

25. A pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds according to claim 23 comprising 1 hydrogen bond acceptor, 1 hydrophobic feature and 1 hydrogen bond donor.

26. A pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds according to claim 25 comprising the following centroids and vectors:

Coordinates	**Hydrogen Bond Acceptor**		**Hydrogen Bond Donor**		**Hydrophobic**
		Vector		**Vector**	
X	-2.73	-2.89	0.93	0.60	-1.66
Y	-1.83	-4.67	-1.69	-4.62	1.06
Z	0.12	-0.84	0.14	0.67	1.16

27. A method for the identification of an selective serotonin reuptake inhibitor compound which does not possess significant inhibitory potency towards CYP2D6 comprising the steps of

(i) generating two- and/or three-dimensional descriptors for an selective serotonin reuptake inhibitor compound;

(ii) inputting said two- and/or three-dimensional descriptors for the selective serotonin reuptake inhibitor compound into the equation of claim 16;

(iii) solving said equation for the inhibitory activity of the selective serotonin reuptake inhibitor compound corresponding to the generated two- and/or three-dimensional descriptors of step (i); and

(iv) designating the compound as not being a significant inhibitor of CYP2D6 activity if the calculated $K_{i\,(apparent)}$ value is greater than 1 μM.

28. A method according to claim 27 where the calculated $K_{i\,(apparent)}$ value is greater than 10 μM.

29. A method according to claim 27 wherein the calculated $K_{i\,(apparent)}$ value of step (iv) is greater than 100 μM.

30. A selective serotonin reuptake inhibitor compound which does not possess significant inhibitory potency towards CYP2D6 identified by the method of claim 27.

31. A pharmaceutical composition comprising an selective serotonin reuptake inhibitor compound, which does not possess significant inhibitory potency towards CYP2D6, according to claim 30.

32. A method of treatment for a condition, disorder or disease for which an selective serotonin reuptake inhibitor compound is therapeutically useful comprising the administration of an selective serotonin reuptake inhibitor compound according to claim 30.

33. A method according to claim 32 wherein the condition, disease or disorder is selected from the group consisting of nausea, asthma, migraine, arthritis, post-operative pain and depression.

34. A method of designing *de novo* compounds that are selective serotonin reuptake inhibitor compounds which do not possess significant inhibitory potency towards CYP2D6 comprising the step of

(i) correlating the three-dimensional descriptors for a pharmacophore model for selective serotonin reuptake inhibitor compounds that possess inhibitory potency towards CYP2D6 with randomly generated molecules having chemical features corresponding to said descriptors; and

(ii) choosing a generated molecule with a CYP2D6 $K_{i\ (apparent)}$ value of 1 μM or greater.

35. A method according to claim 34 wherein the CYP2D6 $K_{i\ (apparent)}$ value is 10 μM or greater.

36. A method according to claim 34 wherein the CYP2D6 $K_{i\ (apparent)}$ value is 100 μM or greater.

37. A method according to claim 34 wherein said molecules having features corresponding to said descriptors are randomly generated from a library of known chemical features and conformational preferences of chemical groups and multiple chemical groupings.

38. A method of designing *de novo* compounds that are selective serotonin reuptake inhibitor compounds which possess an inhibitory potency towards CYP2D6 corresponding to an $K_{i\ (apparent)}$ value of greater than 10 μM comprising the steps of

(i) generating a three-dimensional descriptor for a pharmacophore model for selective serotonin reuptake inhibitor compounds which possess an inhibitory potency towards CYP2D6 corresponding to an $K_{i\ (apparent)}$ value of 10 μM or greater; and

(ii) correlating said descriptors of step (i) with compounds having chemical features corresponding to said descriptors.

39. A computer-readable medium having stored thereon a pharmacophore model for selective serotonin reuptake inhibitor compounds which possess significant inhibitory potency towards CYP2D6 generated in accordance with the method of claim 1.

40. A computer comprising a computer-readable medium according to claim 39.

41. A computer-readable medium having stored thereon a pharmacophore model for selective serotonin reuptake inhibitor compounds which possess significant inhibitory potency towards CYP2D6 generated in accordance with the method of claim 16.

42. A computer comprising a computer-readable medium according to claim 41.

43. A computer comprising a computer-readable medium comprising a pharmacophore model for the inhibitory potency towards CYP2D6 of selective serotonin reuptake inhibitor compounds generated in accordance with the method of claim 1 or 16 for use in the design or screening of a molecule having selective serotonin reuptake inhibitor activity and CYP2D6 inhibitory activity.